Docket No.: 022290.0116C1US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Valerie Legrand et al.

Application No.: 10/826,690 | Confirmation No.: 9585

Filed: April 19,2004 | Art Unit: 1618

For: MICROPARTICULATE ORAL GALENICAL FORM FOR THE DELAYED AND CONTROLLED RELEASE OF PHARMACEUTICAL ACTIVE PRINCIPLES | Examiner: L. Schlientz

DECLARATION OF ANNE-SOPHIE DAVIAUD-VENET

1. My name is ANNE-SOPHIE DAVIAUD-VENET.

2. I have been an employee of Flamel Technologies, S.A. since June 2, 2003.

3. My position at Flamel Technologies, S.A. is Formulation Scientist.

4. I have a Ph.D. in Macromolecules Science and Polymer Materials.

5. I have worked in the area of pharmaceutical compositions for 7 years.

6. I consider myself to be one of skill in the art of oral pharmaceutical compositions for modified release of active principles.

7. I reviewed the office action mailed October 26, 2010 for U.S. Application No. 10/826,690.

8. I also reviewed Li *et al.* (US 2003/0035840), the reference cited by the Examiner in the 35 U.S.C. § 103(a) rejections.

9. I believe the Examiner is alleging it would have been obvious to provide active pellets of the claimed diameter with a coating comprising a pH dependant coating polymer, such as methacrylic acid copolymers or hydroxypropyl methylcellulose phthalate in the range of 3-5 % and lubricant such as glyceryl monostearate in the range of 1-2.5%, as described in Example 1 of Li *et al.*, which would result in the claimed release profile. See, Office Action at page 5.

10. I performed two laboratory experiments to produce coated metformine hydrochloride microparticles of the claimed diameter (205 and 585 μm respectively), where the coating composition showed a ratio of 5.6% glycerol monostearate (compound B) to 16.9% HPMCP (polymer A), i.e. a 0.33:1 weight ratio of B/A, as in Example 1 in Li *et al.* Metformine shows approximately the same solubility as bupropion, found in Example 1 of Li *et al.*, and, therefore, is an appropriate substitute for these experiments. See Experiments 1 and 2 below.

11. I also performed a laboratory experiment to produce coated metformine hydrochloride microparticles of the claimed diameter (521 μm), where the coating contained the same polymer A (HPMCP) and compound B (glycerylmonostearate) as in Experiments 1 and 2, but with a weight ratio of B/A within the claimed range. See Experiment 3 below.

Experiment 1

12. Metformine coated microparticles with the coating composition and weight ratio of B/A of Example 1 of Li *et al.* and the claimed diameter were prepared as follows :

13. Active Microparticles

	% w/w based on the total weight of the Active Microparticles
Metformine hydrochloride	85
Cellulose spheres (Cellet 90 from Pharmatrans – 63/125 μm)	15

14. Active microparticles of metformine were formed by dissolving 1700.0 g of metformine hydrochloride in water. The active drug solution was then sprayed onto 300.2 g of cellulose spheres in a fluidized bed processor with a Wurster insert.

15. Coated Microparticles

	%w/w based on the total weight of the final Coated Microparticles
Metformine microparticles	75
HMPCP 50 (HP-50 from Shin Etsu)	16.9
Acetyltributyl citrate (Citrofol® BII from Jungbunzlauer)	2.5
Glyceryl monostearate (Imwitor® 491 from Sasol)	5.6

16. 90.2 g of hydroxypropyl methylcellulose phthalate and 13.3 g of acetyltributyl citrate were dissolved in a mixture of purified water and isopropyl alcohol. Then 29.9 g of glyceryl monostearate [Imwitor® 491] were introduced into the solution, which was heated up to 70°C. When the components were dissolved, the solution was sprayed onto 400.0 g of the metformine microparticles in a fluidized bed processor with a Wurster insert. The coated microparticles were then dried in the fluidized bed processor for 2 hours with an input air at 55°C and an air flow at 55 m^3/h.

17. The coated microparticles mean diameter in volume was determined by a laser granulometric equipment Mastersizer 2000 of Malvern : 205 µm.

18. Dissolution Testing

19. 5 g of the coated microparticles were then mixed with 1% (w/w) magnesium stearate.

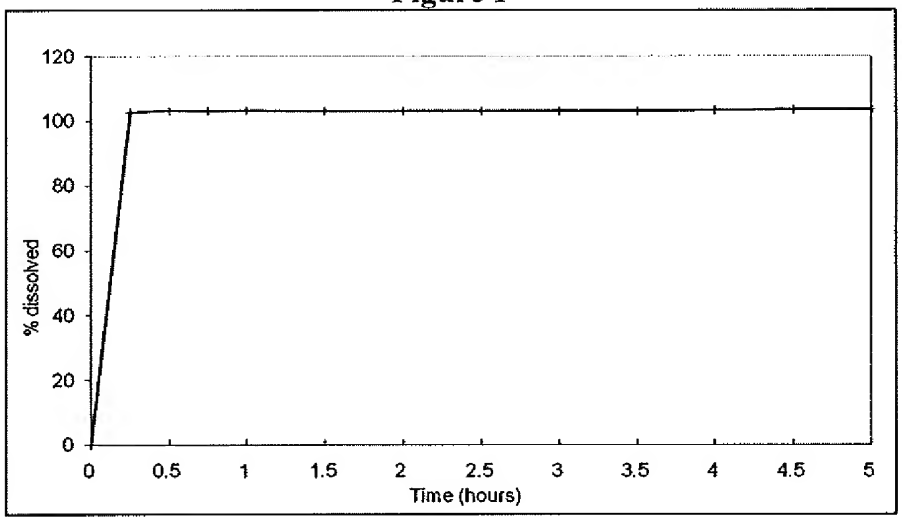
20. The resulting blend of metformine coated microparticles and magnesium stearate was then tested according to the USP dissolution test type 2 at 100 rpm at 37 °C in pH 1.5 medium to determine the percent of the drug dissolved versus time :

Table 1

Time (hrs)	% Dissolved
0	0
0.25	103
0.5	103
0.75	103
1	103
1.5	103
2	103
2.5	103
3	103
3.5	103
4	103
4.5	104

5	104

Figure 1



21. The *in vitro* release profile presented in Figure 1 showed an immediate release behavior, i.e., the whole dose was dissolved in 15 minutes in pH 1.5 medium. No latency phase was observed and all active was dissolved before 0.5 hour. 100% of the total dose was released within 0.5 hour, thus the $t_{1/2}$ corresponding to this release phase was less than 0.5 hour. The metformine coated pellets had a weight ratio B/A equal to 0.33. .

Experiment 2

22. Metformine coated microparticles with coating composition and weight ratio B/A of Example 1 of Li *et al.* and claimed diameter were prepared as follows :

23. Active Microparticles

	% w/w based on the total weight of the Active Microparticles
Metformine HCl	85
Cellulose spheres (Celphere CP 203 from Asai Kasei – 230 µm)	15

24. Microparticles of metformine were formed by dissolving 1700 g of metformine HCl in water. The solution of metformine was then sprayed onto 300 g of cellulose spheres Celphere CP 203 in a fluidized bed processor with a Wurster insert.

25. Coated Microparticles

	%w/w based on the total weight of the Coated Microparticles
Metformine microparticles	75
HMPCP 50 (HP-50 from Shin Etsu)	16.9
Acetyltributyl citrate (Citrofol® BII from Jungbunzlauer)	2.5
Glyceryl monostearate (Imwitor® 491 from Sasol)	5.6

26. 89.2 g of hydroxypropyl methylcellulose phthalate and 13.2 g of acetyltributyl citrate were dissolved in a mixture of purified water and isopropyl alcohol. Then 29.8 g of glyceryl monostearate [Imwitor® 491] were introduced into the solution, which was heated up to 70°C. When the components were dissolved, the solution was sprayed onto 396 g of the metformine core pellets in a fluidized bed processor with a Wurster insert. The pellets were then dried in the fluidized bed processor for 2 hours with an input air at 55°C and an air flow at 55 m^3/h.

27. The pellets mean diameter in volume was determined by a laser granulometric equipment Mastersizer 2000 of Malvern : 585 µm.

28. Dissolution Testing

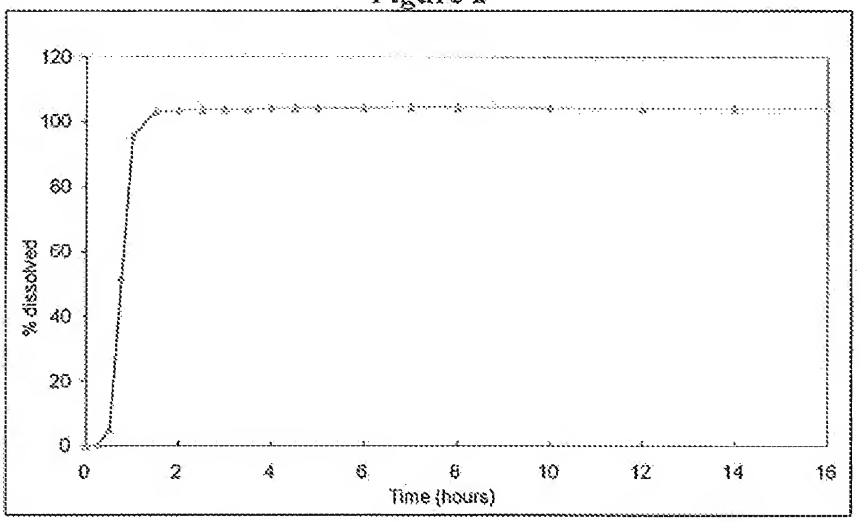
29. 5 g of the coated microparticles were then mixed with 1% (w/w) magnesium stearate.

30. The resulting blend of metformine coated microparticles and magnesium stearate was then tested according to the USP dissolution test type 2 at 100 rpm at 37 °C in pH 1.5 medium to determine the percent of the drug dissolved versus time :

Table 2

Time (hrs)	% Dissolved
0	0
0.25	0.7
0.5	5.3
0.75	52.0
1	95.8
1.5	103.4
2	103.7
2.5	103.8
3	104.0
3.5	104.3
4	104.4
4.5	104.4
5	104.4
6	104.5
7	104.7
8	104.7
10	104.5
12	104.3
14	104.2
16	104.4

Figure 2



31. The release profile presented in Figure 2 determined at pH 1.5 for the metformine coated pellets, which had a weight ratio B/A equal to 0.33, showed a latency phase equal to 0.5 hour and then a release phase which was an immediate release of the whole dose of the active principle. 90% of the total dose was released within 0.5 hour, thus the $t_{1/2}$ corresponding to this release phase was less than 0.5 hour.

Experiment 3

32. Metformine coated microparticles with a mean diameter and a B/A ratio as claimed were prepared by coating the metformine active particles of with the polymer A and compound B as described in Experiment 1 of Li *et al.* as follows:

33. Coated Microparticles

	%w/w based on the total weight of the Coated Microparticles
Metformine microparticles	75
HMPCP 50 (HP-50 from Shin Etsu)	10
Glyceryl monostearate (Imwitor® 491 from Sasol)	15

34. 52.8 g of hydroxypropyl methylcellulose phthalate and 79.2 g of glyceryl monostearate [Imwitor® 491] were dissolved in a hot mixture of purified water and isopropyl alcohol. The solution was then sprayed onto 396 g of the metformine microparticles prepared in Experiment 1 in a fluidized bed processor with a Wurster insert. The coated microparticles were then dried in the fluidized bed processor for 2 hours with an input air at 55°C and an air flow at 55 m^3/h.

35. The pellets mean diameter in volume was determined by a laser granulometric equipment Mastersizer 2000 of Malvern : 521 µm.

36. Dissolution Testing

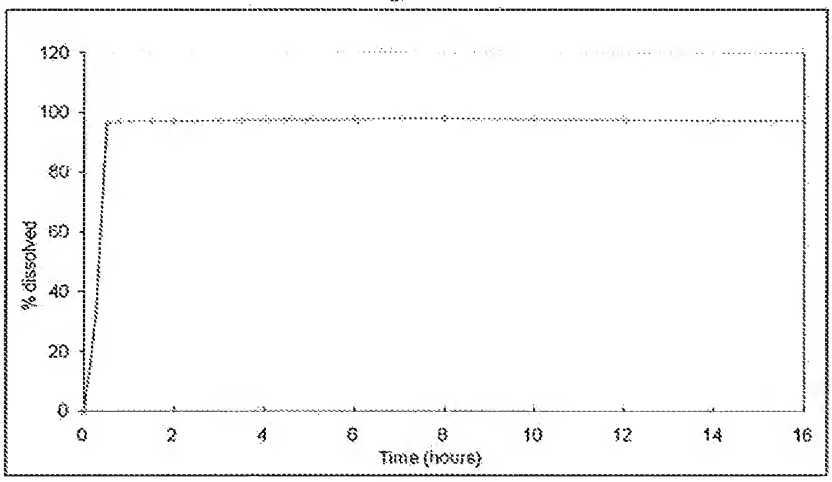
37. 5 g of the coated microparticles were then mixed with 1% (w/w) magnesium stearate.

38. The resulting blend of metformine coated pellets and magnesium stearate was then tested according to the USP dissolution test type 2 at 100 rpm at 37 °C in pH 1.5 medium to determine the percent of the drug dissolved versus time :

Table 3

Time (hrs)	% Dissolved
0	0
0.25	32.1
0.5	96.7
0.75	97.0
1	97.0
1.5	97.1
2	97.1
2.5	97.2
3	97.2
3.5	97.5
4	97.5
4.5	97.6
5	97.6
6	97.7
7	97.9
8	98.0
10	97.8
12	97.5
14	97.4
16	97.3

Figure 3

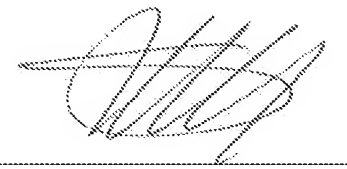


39. The release profile presented in Figure 3 showed an immediate release of the whole dose of the active with no latency phase. The weight ratio B/A was 1.5. All active principle was dissolved within 0.5 hour, thus the $t_{1/2}$ corresponding to this release phase was less than 0.5 hour.

40. In conclusion, using the coating composition and weight ratio B/A of Example 1 of Li *et al.* to produce coated microparticles of the claimed diameter range does not give the

claimed release profile as $t_{1/2}$ was less than 0.5 hours. Modifying the weight ratio B/A of HPMCP and glycerylmonostearate, the coating composition of Example 1 of Li *et al.*, to obtain a weight ratio B/A within the claimed range and produce coated microparticles of claimed diameter range also does not give the claimed release profile as $t_{1/2}$ was less than 0.5 hours.

41. I declare that all statements made of my own knowledge are true and all statements made on information and belief are believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent application.



26 April 2011

Anne-Sophie Daviaud-Venet Date